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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,997	01/04/2001	J. Michael Salbaum	P-NI 4552	4685

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,997	SALBAUM, J. MICHAEL	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-8,11,13 and 15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,12,14 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-20 are pending.

2. Applicant's election with traverse of Group IV, claims 9-15 and 20 drawn to an isolated nucleic acid molecule of SEQ ID NO: 1 encoding Nope polypeptide of SEQ ID NO: 2, filed on 12/30/02, is acknowledged.

Applicant's traversal is on the grounds that the restriction search of the claims of either Group IV or Group V will likely reveal art relevant to the examination of the claims of the either Groups. This is not found persuasive because the isolated nucleic acid molecule of Group IV and the method of detecting Nope nucleic acid are recognized divergent subject matter. Therefore the method of detecting Nope nucleic acids by hybridization and the isolated nucleic acid are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-8 and 16-19 (non-elected Groups I-III and V) and 11, 13 and 15 (non-elected species) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 9-10, 12, 14 and 20 are under examination as they read on an isolated nucleic acid molecule of SEQ ID NO: 1 encoding Nope polypeptide of SEQ ID NO: 2.

5. Applicant's IDS, filed 1/23/02 (Paper No. 6), is acknowledged, however, references 91 and 92 were crossed out as the entire documents were not found. Applicant is invited to produce such documents.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

7. Claims 9-10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 9-10 are indefinite in the recitation of "a modification thereof" because it is unclear whether the "modification" refers to the nucleic acid molecule or to the polypeptide amino acid sequence of SEQ ID NO: 2.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 9-10, 12, 14 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleotide sequence of SEQ ID NO:1 encoding SEQ ID NO:2 for detection assays; does not reasonably provide enablement for any nucleic acid "modification" in claims 9-10; any Nope oligonucleotide **comprising** between 15 and 300 contiguous nucleotides of SEQ ID NO:1 or the antisense strand thereof in claim 12 "; or any kit comprising one or more Nope oligonucleotides **comprising** between 15-300 contiguous nucleotides of SEQ ID NO:1 or the antisense strand thereof in claim 20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses the nucleic acid sequence of SEQ ID NO:1 encoding a polypeptide SEQ ID NO:2 with a disclosed expression during embryonic development in the notochord, in developing skeletal muscles, and later in the ventricular zone of the nervous system. While in the adult brain, Nope is present in hippocampus. (e.g., page 6 at lines 1-5). The instant claims encompass in their breadth *any* nucleic acid *modification*; or *any* nucleic acid comprising "*between 15 and 300 contiguous nucleotides of SEQ ID NO: 1 or the antisense strand thereof*".

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various nucleic acids recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for detection assay. Without detailed direction as to which nucleic acid sequences are essential to the function of the encoded polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of nucleic acid sequences encompassed by the instant claims would useful for the for the detection assay of the nucleic acid of SEQ ID NO:1, other than the nucleic acid of SEQ ID NO:1 encoding SEQ ID NO:2.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects and finally what changes can be tolerated with respect thereto is complex and well outside the

realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant application, it is noted that various mutations, substitutions and the like provide a range of activities, no all which are necessarily predictive of enhanced ability to Nope polypeptide. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to enhanced Nope activity and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of other functional derivatives of Nope. Without sufficient guidance, the changes which can be made in the structure of SEQ ID NO: 1 and 2 and still provide the same properties as Nope is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences, and in turn does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

The term "comprising" in claims 12 and 20 is open-ended, it expands the nucleic acid portions of SEQ ID NO: 1 to include additional non disclosed nucleic acids outside of the 15 to 300 contiguous nucleotides. The instant claim language appears to encompass subsequences. For

example, claims 12 and 20 recite a nucleic acid comprising between 15 and 300 contiguous nucleotides of SEQ ID NO:1 or the antisense strand therof. Such a recitation does not require that the nucleic acid encode the full length sequence set forth in SEQ ID NO:1; but rather encompasses any amino acid sequence comprising either the full length of SEQ ID NO:1 or *any subsequence*. However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:1 would be useful for the detection assay. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:1 would have the function of the full length molecule.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the instantly recited nucleic acid sequences and still encode a polypeptide that maintains the functional properties of the polypeptide of SEQ ID NO:2 is unpredictable, as is the identity of which subsequences would encode a functional polypeptide; thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

10. Claims 9-10, 12, 14 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of the nucleotide sequence of SEQ ID NO:1 encoding SEQ ID NO:2 for detection assays.

Applicant is not in possession of for any nucleic acid "modification" in claims 9-10; any Nope oligonucleotide comprising between 15 and 300 contiguous nucleotides of SEQ ID NO:1 or the antisense strand thereof in claim 12 "; or any kit comprising one or more Nope oligonucleotides comprising between 15-300 contiguous nucleotides of SEQ ID NO:1 or the antisense strand thereof in claim 20.

Applicant has disclosed the nucleic acid of SEQ ID NO: 1 encoding SEQ ID NO:2; therefore, the skilled artisan cannot envision all the contemplated nucleic acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics

coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 9, 10 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Salbaum *et al* (Genomics 64(1):15-23, February 2000) (IDS Ref. No. 86).

Salbaum *et al* teach a 6,176 nucleic acid molecule of instant claimed SEQ ID NO: 1 encoding Nope polypeptide of instant claimed SEQ ID NO:2 (see attached sequence alignment in particular). Salbaum *et al* further teach that an antisense riboprobe transcribed from the Nope gene at positions 3,819-5,682 (see page 16 under Hybridization experiments in particular).

The term "comprising" in instant claim 12 is open ended. It would open up the claim to include the reference 6,176 nucleic acid sequence.

The reference teachings anticipate the claimed invention.

13. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Davies (GenBank Accession No. W33247, 1997) (IDS Ref. No. 22).

Davies teaches a 539 nucleic acid molecule comprising 296 contiguous nucleotide of claimed SEQ ID NO: 1 at positions 4,967-5,262 (see attached sequence alignment in particular).

The term "comprising" in instant claim 12 is open ended. It would open up the claim to include the reference 539 nucleic acid sequence.

The reference teachings anticipate the claimed invention.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salbaum *et al* in view of Darnell *et al.*

The teachings of Salbaum *et al* reference have been discussed, supra.

The claimed invention differs from Salbaum et al reference teachings only by the recitation of a vector in claim 14.

Darnell et al teach that in order to prepare an unlimited amount of a pure gene, a vector containing the gene can be grown in a host cell and DNA extracted. Darnell *et al* also teach an expression vector in order to take advantage of "bacterial tricks" that increase mRNA synthesis to produce large quantities of desired proteins using a eukaryotic vector and host cell, or a prokaryotic and bacterial vector and host cell (page 255-258 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the DNA taught by the Salbaum *et al* reference using the vectors as taught by Darnell *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because a vector containing the a gene that grown in a host cell offers to prepare an unlimited amount of a pure gene as well as to produce large quantities of desired proteins as taught by Darnell *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Salbaum *et al* or Davies in view of U.S Patent No. 6,399,760.

The teachings of Salbaum *et al* and Davies references have been discussed, supra.

The claimed invention differs from Salbaum et al Davies references teachings only by the recitation of a kit comprising one or more Nope oligonucleotides comprising between 15 and 300 contiguous nucleotides of SEQ ID NO:1 or the anti-sense strand thereof.

The `760 patent teaches kits comprising at least one probe nucleic acid, which can be conveniently used in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness. (see Column 36, lines 60-65 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the DNA taught by the Salbaum *et al* or Davies references in a kit as taught the `760 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such a kit can be conveniently used in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness as taught by `760 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. No Claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
March 10, 2003

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